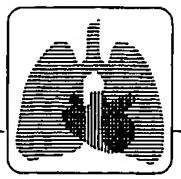

impact of basic research on tomorrow's medicine

Anti-Inflammatory Cytokines*

Steven M. Opal, MD; and Vera A. DePalo, MD

The anti-inflammatory cytokines are a series of immunoregulatory molecules that control the proinflammatory cytokine response. Cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major anti-inflammatory cytokines include interleukin (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, tumor necrosis factor-α, and IL-18 also function as proinflammatory cytokine inhibitors. The nature of anti-inflammatory cytokines and soluble cytokine receptors is the focus of this review. The current and future therapeutic uses of these anti-inflammatory cytokines are also reviewed. ***(CHEST 2000; 117:1162–1172)***

Key words: anti-inflammatory cytokines; cytokines; inflammation; sepsis; septic shock

Abbreviations: GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN-γ = interferon-γ; IL = interleukin; IL-1ra = IL-1 receptor antagonist; LPS = lipopolysaccharide; MHC = major histocompatibility complex; MIP = macrophage inflammatory protein; NF-κB = nuclear factor κB; TGF-β = transforming growth factor-β; Th = T helper cells; TNF = tumor necrosis factor

The human immune response is regulated by a highly complex and intricate network of control elements. Prominent among these regulatory components are the anti-inflammatory cytokines and specific cytokine inhibitors. Under physiologic conditions, these cytokine inhibitors serve as immunomodulatory elements that limit the potentially injurious effects of sustained or excess inflammatory reactions. Under pathologic conditions, these anti-inflammatory mediators may either (1) provide insufficient control over proinflammatory activities in immune-mediated diseases or (2) overcompensate and inhibit the immune response, rendering the host at risk from systemic infection.[1,2]

A dynamic and ever-shifting balance exists between proinflammatory cytokines and anti-inflammatory components of the human immune system. The regulation of inflammation by these cytokines and cytokine inhibitors is complicated by the fact that the immune system has redundant pathways with multiple elements having similar physiologic effects. Furthermore, with the potential exception of interleukin (IL)-1 receptor antagonist (IL-1ra), all the anti-inflammatory cytokines have at least some proinflammatory properties as well. The net effect of any cytokine is dependent on the timing of cytokine release, the local milieu in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine.[3] This is what makes the study of cytokine biology so fascinating (and so frustrating as well!).

Perturbations of this regulatory network of cytokines by genetic, environmental, or microbial elements may have highly deleterious consequences.[4–8] The major anti-inflammatory cytokines and their specific roles in human disease will be the focus of this brief review. These inhibitory cytokines have already proven to be efficacious in a variety of clinical conditions marked by excess inflammation. Their potential therapeutic use in numerous other inflammatory states will also be described.

The principal anti-inflammatory cytokines and cytokine inhibitors are listed in Tables 1, 2. The functional definition of an anti-inflammatory cytokine in this review is the ability of the cytokine to inhibit the synthesis of IL-1, tumor necrosis factor (TNF), and other major proinflammatory cytokines.

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Table 1—*Cytokines With Anti-inflammatory Activities**

Cytokines	Cellular Sources	Major Activities
IL-1ra	Monocyte/macrophage dendritic cells	Specific inhibitor of IL-1α- and IL-1β-mediated cellular activation at the IL-1 cellular receptor level
IL-4	T cells (Th2), mast cells, B cells, stromal cells	Promotes Th2 lymphocyte development; inhibition of LPS-induced proinflammatory cytokine synthesis
IL-6	T cells, B cells, monocytes, PMNs	Inhibition of TNF and IL-1 production by macrophages
IL-10	Monocyte/macrophage, T cells (Th2), B cells	Inhibition of monocyte/macrophage and neutrophil cytokine production and inhibition of Th1-type lymphocyte responses
IL-11	Stromal cells, fibroblasts	Inhibits proinflammatory cytokine response by monocyte/macrophages and promotes Th2 lymphocyte response
IL-13	T cells (Th2)	Shares homology with IL-4 and shares IL-4 receptor; attenuation of monocyte/macrophage function
TGF-β	Constitutively expressed in many cell lines	Inhibition of monocyte/macrophage MHC class II expression and proinflammatory cytokine synthesis

*PMN = polymorphonuclear cell.

Table 2—*Soluble Cytokine Receptors With Anti-inflammatory Activities*

Soluble Receptor	Cellular Sources	Major Activities
Soluble TNF receptor p55 (sTNFRI or sTNFRp55)	Multiple cell lines	Binds to TNF trimers in the circulation, preventing membrane-bound TNF receptor–TNF ligand interactions
Soluble TNF receptor p75 (sTNFRII or sTNFRp75)	Multiple cell lines	Binds to TNF trimers in the circulation, preventing membrane-bound TNF receptor–TNF ligand interactions
Soluble IL-1 receptor type 2 (sIL-1RII)	B cells, neutrophils, bone marrow precursors	Binds to circulating IL-1 ligands in the plasma, preventing IL-1β from binding to the IL-1 receptor type 1
Membrane-bound IL-1 receptor type 2 (mIL-1RII)	B cells, neutrophils, bone marrow precursors	Decoy receptor that lacks intracellular signaling function and competes with type 1 IL-1R for IL-1 ligand binding at the cell membrane
IL-18 binding protein (IL-18BP)	Splenocytes, multiple other cell lines	Soluble extracellular domain of IL-18 receptor that functions as a decoy receptor and binds circulating IL-18

CD4+ T helper (Th) lymphocytes can differentiate into functionally dichotomous subsets of Th cells depending on the microenvironment of the cell. The cytokine-producing CD4+ helper cells are classified into Th1- and Th2-type cells on the basis of the cytokines produced.[9,10] A similar functional system has been recently described with CD8+ cytotoxic T cells (CD8+ T1 and CD8+ T2 cells).[11]

Th1-type cells secrete high levels of IL-2, TNF-α, and interferon-γ (IFN-γ). This activates macrophages and promotes cell-mediated immune responses against invasive intracellular pathogens. Th2-type cells produce a variety of anti-inflammatory cytokines, including IL-4, IL-5, IL-6, IL-10, and IL-13. Both Th1 and Th2 cells produce lesser amounts of TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3. Th2-type cytokines promote humoral immune responses against extracellular pathogens. Mutual cross inhibition between Th1- and Th2-type cytokines polarize functional Th cell responses into cell-mediated or humoral immune responses. Regulation of T-cell activation by the anti-inflammatory cytokines is a crucial early control element in this process (Fig 1).

Major Anti-inflammatory Cytokines

IL-1ra

IL-1ra is a 152-amino-acid protein that functions as a specific inhibitor of the two other functional members of the IL-1 family, IL-1α and IL-1β.[3,12] The human gene for IL-1ra is on the long arm of chromosome 2 in close proximity to the genes for IL-1α and IL-1β. Genetic evidence indicates that IL-1ra diverged from an ancestral IL-1 gene as a partial duplication event early in vertebrate evolution.[12,13] IL-1ra shares approximately 26% amino acid sequence homology with IL-1β and 19% homology with IL-1α. A three-dimensional structure of IL-1ra is similar to IL-1α and IL-1β and exists as a series of anti-parallel β chains held in a tight β barrel configuration.[13]

IL-1ra blocks the action of IL-1α and IL-1β functional ligands by competitive inhibition at the IL-1 receptor level. IL-1ra binds with equal or greater affinity than does IL-1α and IL-1β to the type 1 (80 kd) membrane-bound IL-1 receptor. IL-1ra does not bind with high affinity to the type II (68 kd) IL-1 receptor.[14,15] After attachment of IL-1

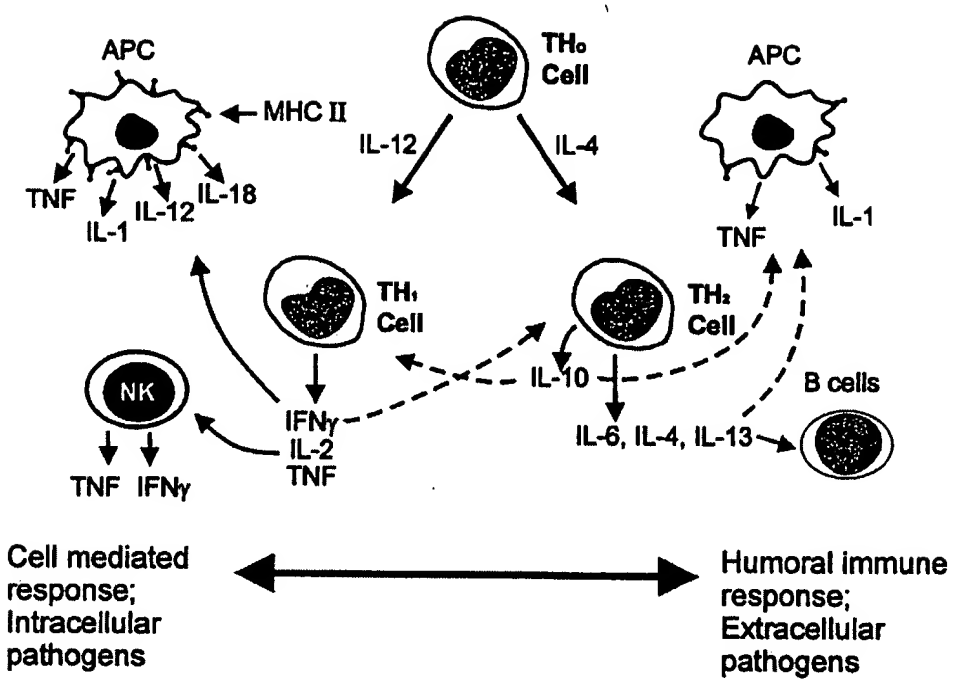

FIGURE 1. The polarization of Th1 and Th2 responses by CD4+ Th cells and the role of the anti-inflammatory cytokines in T-cell differentiation. Solid lines indicate stimulatory pathways, and dotted lines indicate inhibitory pathways. APC = antigen-presenting cell; Th_0 = uncommitted CD4+ Th cell precursor. (See Mosmann et al[9] for review.)

to its receptor, intracellular signaling occurs after a heterodimeric complex is formed between the type 1 receptor and an essential second protein known as IL-1 receptor-accessory protein.[16] IL-1ra will bind with high affinity to the type 1 IL-1 receptor but fails to engage the IL-1 receptor accessory protein. This occupies the membrane-bound IL-1 receptor binding site and prevents cellular activation by IL-1α or IL-1β by steric inhibition.[17]

IL-1ra is produced by monocytes and macrophages and is released into the systemic circulation in > 100-fold excess than either IL-1α or IL-1β after lipopolysaccharide (LPS) stimulation in human volunteers.[3] The synthesis of IL-1ra and IL-1β are differentially regulated at their own promoter sites. Although bacterial LPS stimulates the synthesis of both IL-1β and IL-1ra, other stimuli cause differential release of IL-1ra and IL-1β. The anti-inflammatory cytokines IL-4, IL-6, IL-10, and IL-13 inhibit the synthesis of IL-1β, yet they stimulate the synthesis of IL-1ra.[14]

There is at least one important polymorphism in the genetic regulation of IL-1ra synthesis in human populations.[18] A regulatory region located in intron 2 of the IL-1ra gene varies depending on the number of tandem duplications of an 86-base pair direct-repeat sequence. DNA polymorphisms at this site may determine the synthetic rate of IL-1ra and alter the host response to inflammatory stimuli. Excess IL-1ra synthesis in relationship to IL-1α or IL-1β synthesis has been shown to increase susceptibility to diverse human pathogens such as Lyme arthritis, tuberculosis, and a variety of other infectious diseases.[19–21] Conversely, inadequate local IL-1ra synthesis in the lung may predispose to severe acute lung injury and result in excess lethality in ARDS.[6]

Because IL-1 is such a prominent proinflammatory cytokine in a multitude of systemic inflammatory states, IL-1ra has been extensively studied in clinical trials as a specific IL-1 inhibitor. Despite convincing evidence that IL-1 plays an important role in the pathogenesis of bacterial sepsis,[22,23] the results of IL-1ra therapy in large phase III clinical trials for severe sepsis have been disappointing.[24] Nonetheless, IL-1ra continues to be a promising new treatment for the management of patients with refractory forms of rheumatoid arthritis (Table 3).[25]

IL-4

IL-4 is a highly pleiotropic cytokine that is able to influence Th cell differentiation. Early secretion of IL-4 leads to polarization of Th cell differentiation toward Th2-like cells.[9] Th2-type cells secrete their own IL-4, and subsequent autocrine production of IL-4 supports cell proliferation. The Th2- cell secre-

Table 3—*Current and Future Therapeutic Uses for Anti-inflammatory Cytokines and Soluble Cytokine Inhibitors

Cytokine/Soluble Cytokine Receptor	Clinical Indications
IL-1ra	Rheumatoid arthritis (phase II/III clinical trials)
IL-10	Prevention of acute lung injury (phase I clinical trials); gut ischemia-reperfusion injury (phase I clinical trials); inflammatory bowel disease (phase II clinical trials); rheumatoid arthritis (phase II clinical trials); psoriasis, multiple sclerosis (early phase II clinical trials)
IL-11	Chemotherapy-induced thrombocytopenia (approved indication); inflammatory bowel disease (phase II clinical trials); chemotherapy-induced mucositis (phase II clinical trials); psoriasis (phase I clinical trials)
TNFR (p75):Fc fusion protein	Treatment of rheumatoid arthritis (approved indication)

*TNFR = TNF receptor.

tion of IL-4 and IL-10 leads to the suppression of Th1 responses by down-regulating the production of macrophage-derived IL-12[26] and inhibiting the differentiation of Th1-type cells.[9,10]

IL-4 is a 20-kd glycoprotein produced by mature Th2 cells and cells from the mast cell or basophil lineage. IL-4 drives Th2 responses, mediates the recruitment and activation of mast cells, and stimulates the production of IgE antibodies via the differentiation of B cells into IgE-secreting cells.[26,27]

IL-4 has marked inhibitory effects on the expression and release of the proinflammatory cytokines. It is able to block or suppress the monocyte-derived cytokines, including IL-1, TNF-α, IL-6, IL-8, and macrophage inflammatory protein (MIP)-1α.[26–29] It has also been shown to suppress macrophage cytotoxic activity, parasite killing, and macrophage-derived nitric oxide production.[30] In contrast to its inhibitory effects on the production of proinflammatory cytokines, it stimulates the synthesis of the cytokine inhibitor IL-1ra.[31]

The immunologic effects of IL-4 in the presence of bacterial infection are complex and incompletely understood. IL-4 has been shown to enhance clearance of *Pseudomonas aeruginosa* from lung tissue in experimental models of Gram-negative bacterial pneumonia.[32] In Gram-positive bacterial infection models, IL-4 has been found to act as a growth factor for *Staphylococcus aureus*, resulting in systemic infection and increased lethality from bacterial sepsis.[33] The role of IL-4 in the presence of systemic infections is not adequately defined and will necessitate additional clinical investigation.

IL-4 is able to affect a variety of structural cells. It can potentiate proliferation of vascular endothelium and skin fibroblasts yet decrease proliferation of adult human astrocytes and vascular smooth muscle cells.[26,34] In addition, IL-4 induces a potent cytotoxic response against tumors.[35,36] In a study of 63 patients with stage IV non-small cell lung cancer, data on treatment with recombinant human IL-4 seemed to suggest a possible dose-related response.[37] IL-4 may act by stabilizing disease and modifying tumor growth rates in addition to inducing tumor shrinkage and cell death without causing severe side effects, suggesting a possible adjuvant role for IL-4 in the treatment of malignant diseases.

IL-6

IL-6 has long been regarded as a proinflammatory cytokine induced by LPS along with TNF-α and IL-1. IL-6 is often used as a marker for systemic activation of proinflammatory cytokines.[38] Like many other cytokines, IL-6 has both proinflammatory and anti-inflammatory properties. Although IL-6 is a potent inducer of the acute-phase protein response, it has anti-inflammatory properties as well.[39] Recent evidence generated from IL-6 knockout mice has demonstrated that IL-6, like other members of the gp130 receptor ligand family, acts predominantly as an anti-inflammatory cytokine. After binding to its specific α receptor, IL-6 complexes with the ubiquitous gp130 signal transducing unit. IL-6 belongs to a family of gp130 receptor ligands that includes IL-11, leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M, and cardiotrophin-1. Inasmuch as these peptide molecules use a common cellular receptor, they share many of the physiologic features attributable to IL-6. IL-6 down-regulates the synthesis of IL-1 and TNF.[40,41] IL-6 attenuates the synthesis of the proinflammatory cytokines while having little effect on the synthesis of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β). IL-6 induces the synthesis of glucocorticoids[42] and promotes the synthesis of IL-1ra and soluble TNF receptor release in human volunteers.[43] At the same time, IL-6 inhibits the production of proinflammatory cytokines such as GM-CSF, IFN-γ, and MIP-2.[38] The net result of these immunologic effects place IL-6 among the anti-inflammatory cytokine group.

IL-10

IL-10 is the most important anti-inflammatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including

both IL-2 and IFN-γ. This activity accounts for its initial designation as cytokine synthesis inhibition factor.[44-46] In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage proinflammatory cytokine synthesis.[47,48] IL-10 is primarily synthesized by CD4+ Th2 cells, monocytes, and B cells and circulates as a homodimer consisting of two tightly packed 160-amino-acid proteins.[45,46] After engaging its high-affinity 110-kd cellular receptor, IL-10 inhibits monocyte/macrophage-derived TNF-α, IL-1, IL-6, IL-8, IL-12, granulocyte colony-stimulating factor, MIP-1α, and MIP-2α.[48-50] IL-10 inhibits cell surface expression of major histocompatibility complex class II molecules, B7 accessory molecules, and the LPS recognition and signaling molecule CD14.[46] It also inhibits cytokine production by neutrophils and natural killer cells. IL-10 inhibits nuclear factor κB (NF-κB) nuclear translocation after LPS stimulation[48] and promotes degradation of messenger RNA for the proinflammatory cytokines.[46] In addition to these activities, IL-10 attenuates surface expression of TNF receptors and promotes the shedding of TNF receptors into the systemic circulation.[51,52]

IL-10 is readily measurable in the circulation in patients with systemic illnesses and a variety of inflammatory states.[53,54] IL-10 is present in sufficient concentrations to have a physiologic impact on host responses to systemic inflammation. It has been determined that patients who preferentially express high levels of IL-10 and reduced levels of TNF-α are more likely to die from meningococcemia[55,56] and a variety of other community-acquired infections.[57]

Physiologically inadequate IL-10 responses after systemic injury may have detrimental consequences as well. Low lung concentrations of IL-10 in patients with acute lung injury indicate that ARDS is more likely to develop.[6] The administration of IL-10 in experimental animal models of endotoxemia improves survival.[50] Human volunteers given IL-10 after endotoxin challenge suffer fewer systemic symptoms, neutrophil responses, and cytokine production than placebo-treated control subjects.[58] Moreover, mice who have genetic deletions of the IL-10 gene are more susceptible to endotoxin-induced shock than normal mice.[59] IL-10 generally protects the host from systemic inflammation after toxin-induced injury, but renders the host susceptible to lethality from overwhelming infection in a variety of experimental studies.[60,61] This observation should be kept in mind when administering anti-inflammatory cytokines in clinical medicine.

The IL-10 knockout mouse spontaneously develops a chronic inflammatory enteritis that mimics inflammatory bowel disease in humans.[62] This indicates that endogenous concentrations of IL-10 are important in limiting the inflammatory response to gut-associated bacteria. For this reason, IL-10 is in clinical trials as an anti-inflammatory therapy for inflammatory bowel disease among other potential indications (Table 3).

IL-11

IL-11 is a 178-amino-acid nonglycosylated peptide cytokine that was initially isolated from the hematopoietic microenvironment.[63] IL-11 shares many properties of IL-6, including the common use of the gp130 receptor ligand complex as a signal transduction pathway. IL-11 binds to its own unique IL-11 α receptor and then complexes with gp130 cell membranes of target cells.[64] IL-11 was initially described as a hematopoietic growth factor with particular activity in the stimulation of thrombopoiesis. IL-11 has recently been approved for clinical use as a platelet restorative agent after chemotherapy-induced bone marrow suppression.[65]

It has become clear that IL-11 has important immunoregulatory activities separate from its hematopoietic growth factor potential. IL-11 has been shown to attenuate IL-1 and TNF synthesis from macrophages by up-regulating inhibitory NF-κB (inhibitory NF-κB) synthesis in monocyte/macrophage cell lines. Inhibitory NF-κB prevents NF-κB from translocating to the nucleus where NF-κB functions as a transcriptional activator for the proinflammatory cytokines.[66]

IL-11 has also been shown to inhibit the synthesis of IFN-γ and IL-2 by CD4+ T cells. IL-11 functions as a Th2-type cytokine, with induction of IL-4 and inhibition of Th1-type cytokines.[67] IL-11 does not induce the synthesis of IL-10 or TGF-β. This indicates that IL-11 is a direct inhibitor of Th1 lymphocytes and does not act indirectly through induction of IL-10. IL-11 is rarely measurable in the systemic circulation but has been detected and is physiologically active in localized areas of inflammation, such as inflammatory arthritis or inflammatory bowel disease.[68] IL-11 is currently in clinical trials as an immunomodulator for a number of potential clinical indications (Table 3).

IL-13

IL-13, a potent *in vitro* modulator of human monocytes and B-cell function, is secreted by activated T lymphocytes.[69,70] It is a 132-amino-acid nonglycosylated protein with a molecular weight of about 10 kd. The human IL-13 gene has been mapped in close proximity to the IL-4 gene along a 4.5-kilobase sequence of DNA on chromosome 5q31, suggesting a common ancestral origin.[71] IL-13

and IL-4 share a common cellular receptor (IL-4 type 1 receptor), and this accounts for many of the similarities between these two anti-inflammatory cytokines.[72] IL-4 and IL-13 share only 20% to 25% primary amino acid homology, but the major α-helical regions that are essential for their activity are highly homologous.[69] The principal functional difference between IL-4 and IL-13 lies in their effects on T cells. IL-4 is a dominant mediator of Th2 cell differentiation, proliferation, and activity, whereas IL-13 has minimal effects on T-cell function.[70]

IL-13 can down-regulate the production of TNF, IL-1, IL-8, and MIP-1α by monocytes[69,70] and has profound effects on expression of surface molecules on both monocytes and macrophages.[69] IL-13 up-regulates cell surface expression of β_2 integrins and major histocompatibility complex (MHC) class II antigens and down-regulates CD14 and Fcγ receptor expression. IL-13 inhibits NF-κB activation in macrophages and protects against LPS-induced lethality in animal models.[73–75]

IL-13 suppresses lung inflammatory injury after the deposition of IgG immune complexes.[76–78] Exogenous administration of anti-inflammatory cytokines into the lungs of rats after IgG immune complex deposition reveals that the greatest inhibitory activity is observed by IL-13 and IL-10, followed by IL-4 and IL-6. The potential role of IL-13 in clinical medicine remains to be defined.

TGF-β

TGF-β is synthesized as an inactive precursor and requires activation before exerting its effect.[79] The active molecule is a 25-kd homodimer of two 12.5-kd disulfide-linked monomers. It belongs to a superfamily of > 20 distinct dimeric proteins that share a similar structure.[80] There are three isoforms of TGF-β (designated TGF-β1–3) expressed in mammalian species.

TGF-β is an important regulator of cell proliferation, differentiation, and formulation of the extracellular matrix.[81] *In vitro*, it inhibits growth of ectodermally derived cells.[82] TGF-β induces squamous cell differentiation of human bronchial epithelial cells.[83] TGF-β has been shown to inhibit alveolar type II cell proliferation and to decrease the expression of surfactant protein A in human lung explant cultures and in a human lung adenocarcinoma cell line.[84] TGF-β appears to contribute to the fibroproliferative phase of acute lung injury from a variety of injurious agents.[85] It plays a role in regulating the extracellular matrix by decreasing degradation of matrix proteins through a reduction in protease synthesis and an increase in the synthesis of protease inhibitors.[86]

Like many cytokines, TGF-β has both pro- and anti-inflammatory effects. It functions as a biological switch, antagonizing or modifying the action of other cytokines or growth factors. The presence of other cytokines may modulate the cellular response to TGF-β, and the effect may differ depending on the activation state of the cell.[80] TGF-β is capable of converting an active site of inflammation into one dominated by resolution and repair.[81] TGF-β often exhibits disparate effects with immune-enhancing activity in local tissues and immune-suppressive activity in the systemic circulation.

TGF-β1 suppresses the proliferation and differentiation of T cells and B cells and limits IL-2, IFN-γ, and TNF production. TGF-β1 acts as a monocyte/macrophage deactivator in a manner similar to IL-10. However, TGF-β is less potent an inhibitor than IL-10 and has little or no effect on IL-1 production.[81] The severe and uncontrolled inflammatory reactions observed in the TGF-β1 knockout mouse attests to the physiologic role of TGF-β as an endogenous anti-inflammatory cytokine.[87]

Soluble Cytokine Receptors as Anti-inflammatory Molecules

Both type 1 (p55) and type 2 (p75) receptors for human TNF-α may exist on the cell membrane as a signal-transducing unit or in a soluble form in the extracellular fluid. The extracellular domain of both TNF receptors may be solubilized into the systemic circulation, and they retain the capacity to bind TNF-α ligands at affinity levels that are comparable to those of membrane-bound TNF receptors.[88] Soluble receptors compete with membrane-bound receptors for TNF binding. High amounts of soluble TNF receptors function as specific inhibitors of TNF activity on target tissues. Shedding of membrane-bound TNF receptors by susceptible target tissues also tends to desensitize these tissues to TNF activity.[88–90]

It should be noted that TNF receptors may, under certain circumstances, function as TNF agonists rather than TNF antagonists.[91] This is known to occur specifically with soluble type 2 (p75) TNF receptors. The soluble p75 TNF receptor may bind to TNF-α in the circulation and prolong its circulating half-life. Because TNF-α may readily dissociate from the type 2 receptor, the end result may be prolongation of TNF activity in the systemic circulation with potentially detrimental effects.[92] Both type 1 and type 2 receptors are readily measurable in the circulation in humans under a variety of systemic inflammatory and other pathologic states. The soluble receptor concentrations are sufficient to attenuate systemic TNF activity.[93]

Soluble IL-1 receptors are also measurable under some pathologic states.[13,14] The soluble receptor found is primarily the type 2 receptor (p68) for IL-1. Soluble IL-1 receptors will bind to IL-1α and IL-1β although they do not bind with high affinity to IL-1 receptor antagonist.[14]

The IL-1 type 2 receptor appears to function primarily as a decoy receptor both in its soluble and membrane-bound forms.[15] The type 2 receptor has a short transmembrane domain and intracellular domain and does not have the capacity to activate the signal-transduction pathways. It appears to function as a molecular decoy that prevents interaction of IL-1α and IL-1β with the functional type 1 IL-1 receptor.[14]

The recently described proinflammatory cytokine known as IL-18 also has a soluble receptor that functions to attenuate IL-18 activity.[94] IL-18 is a macrophage product, which is initially synthesized as pro-IL-18. The pro-peptide is cleaved into active IL-18 through caspase-1. This is the same enzyme that activates pro-IL-1β (IL-1β converting enzyme). Activated IL-18 stimulates the synthesis of IFN-γ by CD4+ T lymphocytes and has similar activities as the proinflammatory cytokine IL-12.[95,96]

A soluble receptor for IL-18 known as IL-18 binding protein has been measured in the serum and urine of humans. The IL-18 binding protein lacks a transmembrane domain or intracellular domain and circulates as the extracellular domain of IL-18 receptor. It will bind to IL-18 in the systemic circulation and prevent IL-18 from binding to its membrane-bound receptor. The IL-18 receptor appears to be closely related to the IL-1 receptor. The protein formerly known as IL-1 receptor-related protein now appears to be the principal cell membrane receptor for IL-18 and is now referred to as IL-18 receptor.[96–98]

Physiologic Role of Anti-inflammatory Cytokines and Cytokine Inhibitors

A complex network of cytokines is generated in response to a systemic immune challenge. It is the net effect of interactions between these proinflammatory and anti-inflammatory molecules over time that determines the nature of the immune response in individual patients.[1,4,8,11] Microbial pathogens may actually use components of the cytokine network to their own advantage. A number of DNA viruses synthesize soluble TNF receptor and IL-1 receptors.[99,100] Epstein-Barr virus mediates the synthesis of viral IL-10 in infected human B cells.[101] These viral-induced anticytokine strategies appear to assist the virus in the promotion of viral replication and evasion of host-derived clearance mechanisms.

Several bacterial pathogens have the capacity to alter host cell cytokine synthesis, degrade proinflammatory cytokines, or use cytokine receptors as portals of entry for cellular invasion.[102] Pathogenic microorganisms have evolved a variety of ingenious mechanisms to disrupt host defense mechanisms. Manipulation of the cytokine networks to the advantage of the invading pathogen offers a further example of the importance of proinflammatory cytokines in the protection against microbial invasion.

Administration of inhibitors of proinflammatory cytokines (antibodies, soluble receptors, and anti-inflammatory cytokines) in experimental models generally provides an advantage in systemic toxicity models such as endotoxin challenge studies.[22,23] However, in localized infection models, inhibitors of the proinflammatory cytokine system may be detrimental to the host and precipitate overwhelming infection with excess mortality.[7] This is particularly true in the absence of appropriate antimicrobial therapy against the invading microbial pathogen.[7,46] The dichotomous nature of anti-inflammatory cytokine responses in experimental systems is commonly observed in cytokine biology. Inadequate concentrations of anti-inflammatory cytokines result in excess inflammation, yet excess anti-inflammatory cytokine concentrations disrupt clearance mechanisms of microbial pathogens in the host.

IL-10, soluble TNF receptors, and IL-1ra may be found in high concentrations in the plasma of patients with sepsis.[2,54] Nonetheless, these anti-inflammatory agents must be present in far greater concentrations than those of proinflammatory cytokines to inhibit their actions. Systemic concentrations of soluble cytokine inhibitors IL-1ra and IL-10 indicate that they are of sufficient magnitude to at least partially inhibit proinflammatory cytokine action.[54,88,89,103] These results suggest that there may well be a physiologic role for anti-inflammatory cytokines and soluble cytokine receptors in the face of systemic inflammation.

Recent evidence indicates that individuals differ in their susceptibility to systemic infection and inflammatory states on the basis of their cytokine profiles and genetic background. Patients and first-degree relatives of patients with meningococcemia are more likely to have fatal infections if they have high ratios of IL-10 to TNF-α.[5] Similarly, patients with high ratios of TNF to soluble TNF receptors are at increased risk of having lethal meningococcal infections.[104]

Allelic polymorphism within the second intron of the IL-1ra gene indicates that individuals who have the IL-1ra A2 allele have a greater propensity to develop severe sepsis than do patients with other IL-1ra alleles.[21] A polymorphism in a regulatory

region of the human TNF-β gene is associated with excess risk of death caused by sepsis (the TNF B2 homozygous genotype).[105] Mira and colleagues[106] have recently described differences in septic shock susceptibility and mortality associated with a polymorphism at the TNF-α promotor site in human populations. Individuals born with mutations in the genes for the IFN-γ receptor[107] or IL-12 receptor[108] are highly susceptible to lethal infections caused by mycobacterial infection. These studies make it clear that alterations in cytokine networks can have a significant impact on the human host response to a variety of infectious agents and inflammatory states.

Despite complexities inherent in the human immune response, therapeutic intervention with specific cytokine inhibitors or anti-inflammatory cytokines has already been shown to have significant clinical benefits.[65,109] Several of these agents are already approved for clinical use, and others are undergoing extensive clinical trials for a variety of inflammatory disease states (Table 3).

It is fully anticipated that carefully performed clinical studies in selected patient populations will demonstrate efficacy of these immunomodulatory agents in human disease. The ability to rapidly assess the state of the human immune response and regulate this response in the presence of a variety of human disease states has been the goal of immunologists for the past century. Advances in human genetics and immunobiology now provide an opportunity to capitalize on recent discoveries in basic immunology and cytokine biology. It should soon be possible to intelligently use these immunoregulatory cytokines to the benefit of our patients. It is likely that anti-inflammatory cytokines and specific cytokine inhibitors will increasingly find their way into standard clinical practice as we enter the next millennium.

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